CHEMICAL RIGHT-TO-KNOW WORKSHOP

TOPIC #2: CATEGORIES

Guidance for Development of Chemical Categories in the HPV Challenge Program

U.S. Environmental Protection Agency
Office of Pollution Prevention and Toxics
Risk Assessment Division

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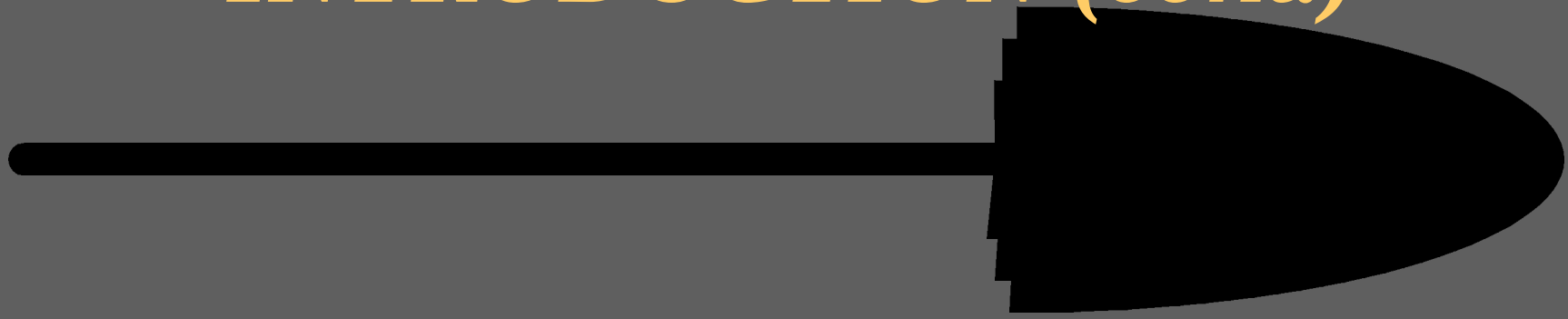
OVERVIEW OF TALK

- ✔ **Introduction**
- ✔ **Definition**
- ✔ **Proposed General Approach**
- ✔ **Content of Category Proposals**
- ✔ **Evaluation and Closure of Category Approach**
- ✔ **Examples**

INTRODUCTION

- ✔ **The HPV Challenge Program is designed to develop screening-level hazard information on approximately 2,800 HPV chemicals.**
- ✔ **The large number of chemicals makes it important to reduce the number of tests where scientifically justifiable.**
- ✔ **One approach is to test some closely related chemicals as a group, or category, rather than test them as individual chemicals.**

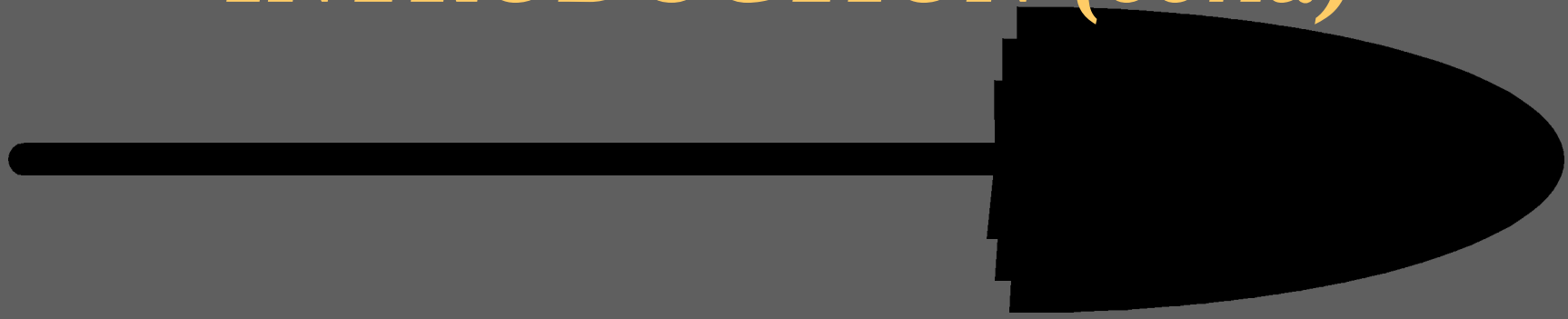
INTRODUCTION (cont.)



Perceived benefits from the use of the category approach:

- ➜ **The public will be informed earlier about potential hazards of HPV chemicals;**
- ➜ **There is an economic savings since less testing may be needed; and**
- ➜ **A reduction in testing will result in fewer animals used to test a category of chemicals.**

INTRODUCTION (cont.)



In the category approach, not every chemical needs to be tested for every SIDS endpoint.

➜ **Test data compiled for a category must support a screening-level hazard assessment of the category and its members.**

➜ **The final data set must allow one to assess the untested endpoints, ideally by interpolation.**

DEFINITIONS

✔ **A chemical category is a group of chemicals whose physicochemical and toxicological properties are likely to be similar, or follow a regular pattern (as a result of structural similarity).**

✔ **The similarities should be based on the following:**

- ➜ **a common functional group (e.g., aldehyde, epoxide, ester, etc.); and**
- ➜ **an incremental and constant change across the category; or**
- ➜ **the likelihood of common precursors and/or breakdown products, via either physical or biological processes, which result in structurally similar chemicals.**

Things to keep in mind.....

THE US EPA CATEGORY GUIDANCE DOCUMENT REFLECTS THE EXTENT OF OPPT'S EXPERIENCE IN DEVELOPING CATEGORIES IN THE SIDS PROGRAM

THE CATEGORY GUIDANCE DOCUMENT IS A "LIVING DOCUMENT"

GENERAL APPROACH FOR DEVELOPING CATEGORIES FOR THE HPV CHALLENGE PROGRAM

STEP 1

Identify structure-based category

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▼

STEP 2

Gather published and unpublished literature for each category member

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▼

STEP 3

Evaluate available data for adequacy

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▼

STEP 4

Construct a matrix of SIDS endpoints vs. category members and indicate in the cells of the matrix whether data are available

▼

▼

STEP 5

Evaluate matrix data patterns

A. Substantial data, but no pattern exists: proposed category not appropriate

B. Substantial data with good correlation: category appropriate; prepare test plan

STEP 6

Make category proposal available for public review and finalize test plan

STEP 7

Carry out proposed testing

STEP 8

Add new data and evaluate with existing data. If category holds, finalize report. Otherwise, re-evaluate category approach and determine appropriateness

CONTENT OF CATEGORY PROPOSALS

Category proposals should include:

- ✔ **category definition**
- ✔ **category rationale**
- ✔ **testing scheme**

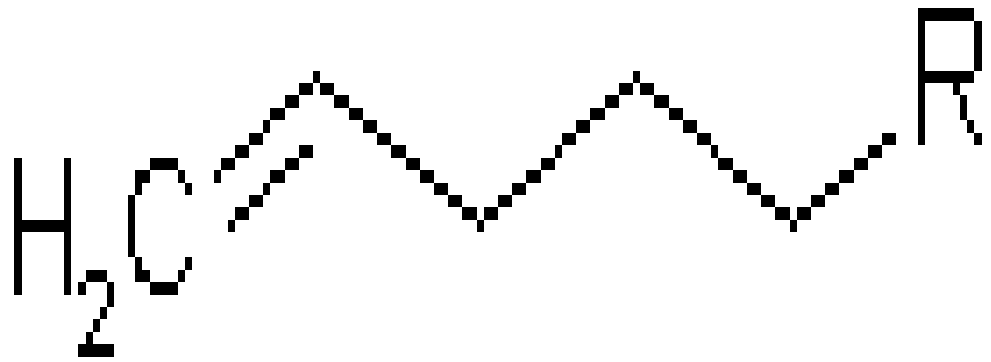
EVALUATION AND CLOSURE OF CATEGORY APPROACH

Once proposed testing done, evaluate data:

- ✔ **if new data support proposed category - submit final report**
- ✔ **if new data do not support proposed category - a reevaluation of category approach should occur**

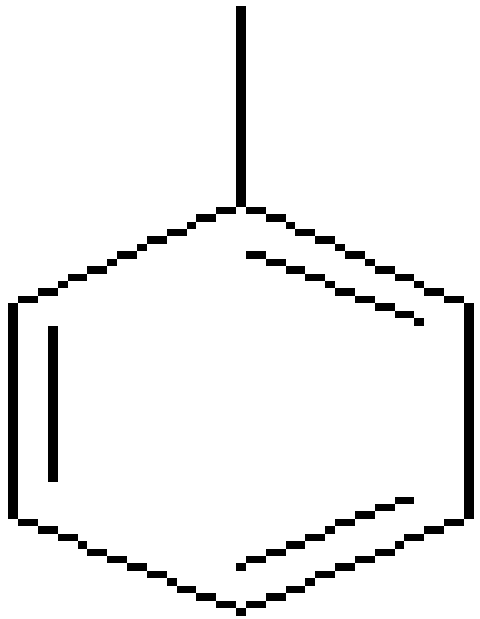
EPA'S EXPERIENCE IN CREATING CATEGORIES FOR TESTING PURPOSES: OECD SIDS EXAMPLES

- **A. Alpha-olefins - discrete chemicals with an incremental and constant change across the category;**
- **B. Linear alkyl benzenes - family of mixtures; and**
- **C. Brominated diphenyl ethers - family of congeners.**



R = CH3, n-Propyl, n-Pentyl, n-Heptyl, n-Nonyl

$$CH_3 - (CH)_x - CH - (CH)_y - CH_3$$



Where $x + y = 7\text{-}13$ and $x = 0\text{-}7$

Alpha-Olefins: Matrix of Available and Adequate Data					
Test Type	**Hexene**	**Octene**	**Decene**	**Dodecene**	**Tetradecene**
Physicochemical Properties					
Part. Coeff.	√	-	√	√	-
Water Sol.	-	-	-	-	√
Environmental Fate					
Biodegrad.	√	-	√	√	√
Envir. Tran.	-	-	-	-	-
Ecotoxicity					
Acute Fish	√	-	√	√	-
Acute Daphnid	√	-	√	√	-
Alga	√	-	√	√	-
Terrestrial	-	-	√	-	-
Human Health Effects					
Acute (O,I,D)	√	√	√	√	√
Repeated Dose	√	√	-	-	-
Genetox (bact)	√	√	√	√	√
Genetox (non-bact)	√	√	-	√	√
Genetox (in vivo)	√	-	-	-	-
Repro/Dev	-	-	-	-	-

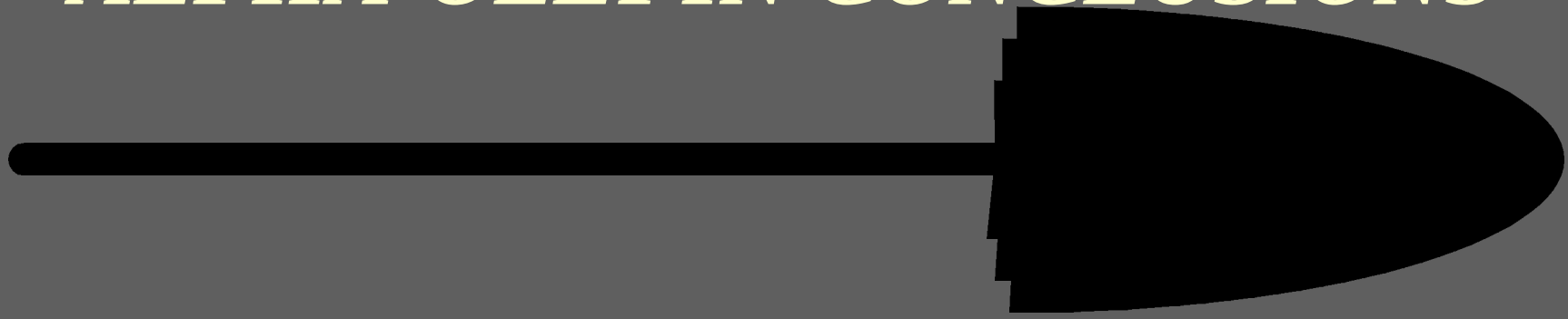
Alpha-Olefin Proposed SIDS Test Plan					
Selected SIDS Endpoint	**Hexene**	**Octene**	**Decene**	**Dodecene**	**Tetradecene**
Water Sol.	-	-	-	-	√/+
Acute Fish	√/+	-	√/+	√/+	-
Acute Daphnid	√/+	-	√/+	√/+	-
Acute Algae	√/+	-	√/+	√/+	-
Repeated Dose	√/+	√/+	-	-	-[1]
Repro/Dev	-	-	-	-	-[1]

[1] A combined repeated dose and reproductive/developmental toxicity screen study design was recommended.

Results of Alpha-olefin SIDS Category Testing					
Selected SIDS Endpoint	**Hexene**	**Octene**	**Decene**	**Dodecene**	**Tetradecene**
Water Solubility	50 mg/L	(4.1 mg/L)	-	-	0.0004 mg/L
Acute Algae	No effect at saturation				
Acute Fish	5.6 mg/L (LC_{50})	(4.8 mg/L) (LC_{50})	No effect at saturation		No effect at saturation
Acute Daphnid	10 mg/L (NOEC)	($3 < EC_{50} < 10$)	No effect at saturation		No effect at saturation
Repeated Dose	$NOEL_{oral}$ = 101 mg/kg (males) and >1000 mg/kg (females)	NOEL = 50 mg/kg (males)	-	-	$NOEL_{oral}$ = 100 mg/kg (males) and >1000 mg/kg (females)
Repro/ Developmental	$NOEL_{repro}$ and $NOEL_{dev}$ = >1000 mg/kg	-	-	-	$NOEL_{repro}$ and $NOEL_{dev}$ = >1000 mg/kg

Interpolation of Results of Alpha-olefin SIDS Category Testing					
Selected SIDS Endpoint	**Hexene**	**Octene**	**Decene**	**Dode-cene**	**Tetradecene**
Water Solubility	50 mg/L	(4.1 mg/L)	**0.0004 < WS < 4.1**		0.0004 mg/L
Repeated Dose	$NOEL_{oral}$ = 101 mg/kg (males) and > 1000 mg/kg (females)	NOEL = 50 mg/kg (males)	***SIMILAR RESPONSE EXPECTED***		$NOEL_{oral}$ = 100 mg/kg (males) and >1000 mg/kg (females)
Repro/ Develop-mental	$NOEL_{repro}$ and $NOEL_{dev}$ = > 1000 mg/kg	***SIMILAR RESPONSE EXPECTED***			$NOEL_{repro}$ and $NOEL_{dev}$ = > 1000 mg/kg

ALPHA-OLEFIN CONCLUSIONS



Existing and new data allow the characterization of aquatic toxicity and human health endpoints using a category approach

Thus, new testing of all members is not necessary for those endpoints.

Example B: Linear Alkylbenzenes

Table B-1: Assignment of LAB SubCategories					
LAB Formulation	Carbon Chain Length for Substituted Alkyl Group (Numbers represent percent of total)				
	C_{10}	C_{11}	C_{12}	C_{13}	C_{14}
Nalkylene 500	21	39	31	7	<1
Nalkylene 500L	20	44	31	5	<1
Alkylate 215	16	43	40	1	<1
Nalkylene 550L	14	30	29	20	7
Alkylate 225	7	25	48	19	1
Nalkylene 575L	9	17	20	30	15
Nalkylene 600	<1	1	23	50	25
Nalkylene 600L	<1	1	23	50	25
Alkylate 230	1	2	16	50	30

STEP 4: Matrix of Available and Adequate Data on LAB CategoryMembers[1]

LAB Formulation	Environ-mental Fate	Ecological Effects		
		Fish Acute	Daphnid Acute	Daphnid Chronic
Nalkylene 500	-	-		
Nalkylene 500L				
Alkylate 215	√	√	√	√
Nalkylene 550L	-	-		
Alkylate 225	√	√	√	-
Nalkylene 575L	-	-		
Nalkylene 600				
Nalkylene 600L				
Alkylate 230	√	√	√	√

Evaluation of Matrix Data Patterns for LAB Category				
LAB Formulation	Environmental Fate	Ecological Effects		
		Fish Acute	Daphnid Acute (EC_{50}) (Nominal)	Daphnid Chronic
Nalkylene 500	Similar degradation expected	Similar response expected		
Nalkylene 500L				
Alkylate 215	**56%**	**> Water solubility**	**80 ppb**	**7.5 to 15 ppb**
Nalkylene 550L	Similar degradation expected	Similar response expected		
Alkylate 225	**61%**	**> Water solubility**	**9 ppb**	**Not tested**
Nalkylene 575L	Similar degradation expected	Similar response expected		
Nalkylene 600	Similar degradation expected	Similar response expected		
Nalkylene 600L				
Alkylate 230	**56%**	**> Water solubility**	**10 ppb**	**13 to 23 ppb[3]**

LINEAR ALKYL BENZENE CONCLUSIONS

Existing and new data allow the characterization of environmental fate and aquatic toxicity endpoints using a category approach

Thus, new testing of all members is not necessary for those endpoints.

Remember…….

➜ **Test data compiled for a category must support a screening-level hazard assessment of the category and its members.**

➜ **The final data set must allow one to assess the untested endpoints, ideally by interpolation.**